Digestive Care, Incorporated

June 24, 2004

Food and Drug Administration (FDA)
Center for Drug Evaluation and Research (CDER)
Dockets Management Branch (HFA-305)
5630 Fishers Lane, Room 1061
Rockville, MD 20852

RE: DOCKET NO. 2003D-0206 (2003N-0205)
"EXOCRINE PANCREATIC INSUFFICIENCY DRUG PRODUCTS - DRAFT GUIDANCE FOR SUBMITTING NDAs"
FEDERAL REGISTER, VOL. 69, NO. 82, APRIL 28, 2004

Dear FDA Representative:

Enclosed please find two originals of DCI's response to the Draft Guidance, as referenced above, which has also been submitted electronically.

If you have any questions or need additional information or clarification, please do not hesitate to contact my office at 610-882-5950.

Sincerely,

TIBOR SIPOS, Ph.D.
President

TS/rl
Encl.

2003N-0205 C2

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Dear FDA Representative:

Digestive Care, Inc. (DCI), manufacturer of PANCRECARB® (pancrelipase) Delayed-Release Capsules, wishes to comment on the proposed guidance documents for submitting NDA for Exocrine Pancreatic Insufficiency Drug Products, dated March 26, 2004.

DCI appreciates the fact that the Agency recognizes these enzyme products have been safely and effectively used for decades. At the same time, DCI fully supports the spirit and initiative captured in this document and understands FDA's continuing role in applying rigorous scientific standards to these products while maintaining market access to all patients. We would, however, like to address several items in this guidance document that we feel need further consideration. These items could impose insurmountable barriers to implementation and could add significant cost increases without any added safety or efficacy benefits. Before addressing these comments, allow me to first provide a brief introduction.

Credentials: Tibor Sipos, Ph.D., President of DCI:

Over the past 35 years, I have been directly involved in the development of Pancreatic Enzyme Products (PEPs). I am the original inventor and developer of the pancrelipase containing enteric-coated microspheres which were first marketed in 1978 by Johnson & Johnson (Ortho-McNeil) under the trade name of PANCREASE®. Also, I am the original inventor of the bicarbonate-buffered and enteric-coated pancrelipase microspheres marketed by DCI under the trade name of PANCRECARB®. During the research and development (pharmaceutical and clinical) phase of these two successful products, I had the privilege and honor to directly interact with eminent clinicians in the design and establishment of clinical methodology in

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demonstrating the efficacy of pancrelipase products to control steatorrhea in chronic pancreatitis and cystic fibrosis patients.

In addition, I directed the enzymatic characterization of bile juices obtained from the duodenum and upper intestine of chronic pancreatitis and cystic fibrosis patients. These bile juices were collected using a triple-lumen gastrointestinal tube. During these studies, I helped to develop clinical methodologies for the demonstration of bioavailability of exogenously administered pancrelipase products in the upper intestine. More recently, I partially supported clinical research studies to determine the fate of exogenously administered enteric-coated pancrelipase products in the entire intestine of adult cystic fibrosis patients by employing a seven-lumen gastrointestinal tube with suction ports positioned in the stomach, duodenum, upper, middle and lower intestine.

It is on the basis of the three plus decades of direct involvement in research, clinical development and commercialization of these products, that I offer the following comments on these proposed guidelines.

COMMENTS ON DRAFT DOCUMENT

Chemistry, Manufacturing, and Controls Section of the Application:

- *Classical biologicals are recognized in ICH guidelines as complex mixtures requiring different characterizations than highly purified biologicals.*

As this section refers to various ICH guidelines, it is important to note the historical development of some of these guidelines as they pertain to "classical" biologicals, which can be characterized as complex mixtures in contrast to highly purified products (such as rDNA). Although the original focus for these guidelines was on all biological products, experts have acknowledged that for classical biologicals, the evaluation of quality should focus on historic safety and potency. As a result, a consensus was reached to restrict the application of the guidelines to products amenable to a high degree or purity, and address the requirements for classical biologicals on a case-by-case basis.

Recognition of the complexity inherent in the quality of these classical biologicals can be seen in present guidelines as per the examples indicated below.

ICH Q6B:
"1.3 Scope

The principles adopted and explained in this document apply to proteins and polypeptides, their derivatives, and products of which they are components (e.g., conjugates). These proteins and polypeptides are produced from recombinant or non-recombinant cell-culture expression

systems and can be highly purified and characterized using an appropriate set of analytical procedures.

The principles outlined in this document may also apply to other product types such as proteins and polypeptides isolated from tissues and body fluids. To determine applicability, manufacturers should consult with the appropriate regulatory authorities.

This document does not cover antibiotics, synthetic peptides and polypeptides, heparins, vitamins, conventional vaccines, cells, whole blood, and cellular blood components. ..."

And

"Historically, the relative purity of biological products has been expressed in terms of specific activity ..."

ICH Q7A:
"Impurity profiles are normally not necessary for APIs from herbal or animal tissue origin."

No doubt these conclusions arose from insights into the difficulties associated with applying conventional standards and controls for purity, stability, and specifications used for chemically synthesized drugs to classical biologicals. As an example, ***the USP specifications for chorionic gonadotropins and menotropins are 80% - 125% for both drug substance and drug product (USP 27, pg. 882 and 1158), a much wider range than expected for synthesized drugs. The USP recognizes lipase specification for Pancrelipase Delayed-Release Capsules of not less than 90% and not more than 165% of the label claim (USP 27, pg. 1402).***

DRUG SUBSTANCE:

While we shall leave much of the detailed response for the drug substance to the Active Pharmaceutical Ingredients (API) manufacturers, we wish to address certain items in this section since manufacturers must confirm specifications prior to formulation.

Identification and Characterization of Pancrelipase Drug Substance:

- *Lipase activity is an absolute criteria for product activity and identity.*
- *Enzymatic activity for other key enzymes are useful characterizations but there is no practical way to impose or force specifications on ratios of multiple enzymes.*
- *Advanced biochemical techniques (e.g. HPLC, SDS-PAGE electrophoresis, Isoelectric-focusing) are good research tools but are unsuitable for routine characterizations of such a complex biological extract as pancrelipase. Pancrelipase drug substance contains water-soluble and non-soluble forms of activity which will not be adequately addressed by numerous analytical assays.*
- *IR and UV methods could be useful characterization methods.*

Pancrelipase drug substance is available in two different lipase potencies from Scientific Protein Labs (SPL). The two drug substances are: "Pancreatic Enzyme Concentrate (PEC)" with approximately 50 USP units of lipase activity, and "Pancreatic Enzyme Concentrate High Lipase (PEC-HL)" with approximately 100 USP units of lipase activity.

Pancrelipase is isolated from the pancreatic glands of pigs by a series of extraction and purification steps. Pancrelipase contains proteins, carbohydrates, nucleic acids, lipids, minerals, and complex tissue components. The proteins which possess biological activity are further defined as enzymes, *e.g.* lipase, protease, amylase, *etc.*; or as hormones, *e.g.* glucagons, insulin, *etc.* Most of the enzymes are secreted as zymogens (inactive precursors) which need to be activated by limited proteolysis to active enzymes. The conversion of zymogens to active enzymes proceeds through a highly complex sequence of enzymatic steps. These steps give rise to multi-components of pancrelipase products with variable enzyme ratios and enzyme potencies, *e.g.* ratios of 1:4:4 to 1:8:5 for PEC and 1:3:3 to 1:5:3 for PEC-HL (lipase:amylase:protease) and enzymatic activities of 40 to 70 USP units/mg of lipase for PEC and 80-120 USP units/mg of lipase for PEC-HL with activities of 180 - 460 USP units/mg of amylase and 120-400 USP units/mg of protease, respectively.

Foremost, the characterization and purity of the drug substance for classical biologicals are daunting tasks. Use of methods described in the proposed guidelines would yield dozens of peaks or bands and it would be extremely difficult or impossible to completely determine which of these peaks or bands are part of the active component and which do not contribute to its overall activity. ***Guidelines Q7A for API already recognizes that impurity profiles from animal tissue origin is an unnecessary step*** *(Section XI B. p. 18).*

Furthermore, both PEC and PEC-HL contain water-soluble and water-insoluble components. The proportion of water-soluble components of PEC is approximately 70% and of PEC-HL is approximately 80-85 %. Lipase activity is distributed between the water-soluble and the water-insoluble portions in a proportion of 45% to 55% in PEC, and 65% to 35% in PEC-HL, respectively. Because lipase activity is present as water-soluble enzymes and also as water-insoluble enzymes, the potency of pancrelipase needs to be assayed as a dispersion in the assay media. Hence, demonstration of catalytic activity via ***lipase potency is the absolute criteria for product activity and identity. Identification and characterization of pancrelipase needs to be based on catalytic activity; e.g. able to hydrolyze lipid substrate (triglycerides) into free fatty acids and monoacyl glycerol.***

The proposed guidelines for the identification of pancrelipase suggest the use of the following methods: HPLC, SDS-PAGE electrophoresis, isoelectric-focusing and other advanced biochemical techniques. These proposed methods are excellent research tools but have limited use in the identification of the pancrelipase drug substance. We would also like to point out that the employment of any one of these techniques is only suitable for the fingerprint analysis of the water-soluble fraction of pancrelipase, while completely ignoring the water-insoluble

fraction with a substantial number of biological active components. When the soluble fraction of pancrelipase is subjected to isoelectric focusing in ampholine containing gel in one dimension, one can identify at least 27 clearly separated and Coomassie brilliant blue, R-250 stained bands. If the electrophoretic separation continues into the second dimension, the initial 27 bands further separate into multiple bands of extreme complexities. The identification of the initial 27 bands as to their catalytic activity; *e.g.* lipase, protease, amylase, *etc.* however, are not known. In my expert opinion, ***the identification of the protein bands after separation by isoelectric focusing, SDS-PAGE electrophoresis or HPLC for biological activity is an extremely complex, labor-intensive and expensive process and is impractical for the routine identification and characterization of pancrelipase raw material. Therefore, these separation techniques should not be required for the identification and characterization of pancrelipase.***

The enzymes in question for pancrelipase, *e.g.* lipase, amylase and protease, are proteins that are composed of amino acids linked together by peptide bonds. Peptide bonds exhibit characteristic absorption bands in the infra-red (IR) spectrum. Thus, ***we recommend the use of the IR spectrophotometric method, employing the KBr pellet technique for the physico-chemical identification and characterizations of pancrelipase***. The IR/KBr method is suitable for the simultaneous identification of pancrelipase whether it contains the water-soluble or the water-insoluble portion of pancrelipase. If there is further interest to characterize the water-soluble portion of pancrelipase, one may employ UV spectrophotometric analysis at 205-210 nm, 260 nm and 280 nm for peptide bond absorption, nucleic acid, and protein concentrations, respectively (Baily JL., Techniques in Protein Chemistry, 2nd Ed., pp. 342-346, Elsevier Publishing Co., 1967). Ratios at 280/260 nm would provide indications for the presence of nucleic acid contamination in pancrelipase products that may be further used to estimate the possible purine load per dosage when the product is prescribed to a patient. Likewise, the soluble protein content of pancrelipase may also be determined by employing the Bradford colorimetric assay using Coomassie Brilliant Blue, R-210 for the assay which only takes ten (10) minutes to complete (Methods in Enzymology 182: 50-69, 1990).

Establishing enzyme ratio specifications for lipase, amylase, and protease are not practical and is unachievable for the reasons cited above; *e.g.* the extreme complexity of the zymogen activation process. We have reviewed our historical files of pancrelipase drug substance over a decade and find greatly varied ratios of lipase:amylase:protease of 1:4:4 to 1:8:5 for PEC and 1:3:3 to 1:5:3 for PEC-HL, respectively.

Removal/Inactivation of Viral Agents:

- *There is no evidence of pig viruses being problematic for humans and this is not done for the food chain.*
- *Exhaustive removal will significantly modify the API, adding significant costs and increasing the potential for additional required characterizations, including a potential for new safety and efficacy studies.*

Based on the historical safety of porcine-derived pancrelipase products, and the lack of any known dangers of the porcine viruses contained in pancrelipase products, leads us to believe that extra processing steps for exhaustive viral inactivation are not necessary. It is well known that lipases are very sensitive to changes resulting from heat, moisture, solvents, or pH. Use of viral inactivating agents may most likely also have undesirable effects causing net degradation of lipase or selectively and independently on any of the components of pancrelipase: lipase, amylase, or protease. The FDA has repeatedly emphasized that toxicity studies are not required for pancrelipase, changes to processing that alter the API may have unforeseen ramifications in terms of the safety/efficacy profiles of the drug substance itself.

Cost considerations are also a major concern for this section. No doubt that characterization, impurity profiling/testing and viral clearance requirements as outlined in the guidance document would add considerable cost to the drug substance. When this cost is added to the potential cost outlined for the drug product, the overall increase in cost to the patient will, in all likelihood, be at least 50%. It is therefore important to consider a value-added approach for patients who have, and will continue to use, these products for dozens of years and may have to bear these undue hardships.

DRUG PRODUCT

Identification and Characterization of Pancrelipase Drug Product:

- *Enzymatic activity for key enzymes provides appropriate product identification.*
- *Lipase activity is an absolute criteria for product activity and identity.*
- *There is no practical way to impose specifications on ratios of multiple enzymes.*
- *IR and UV spectrophotometric methods can provide useful characterizations.*

We recommend the use of IR spectrophotometric methods, employing the KBr pellet technique for the physico-chemical identification and characterizations of pancrelipase in the drug product.

We recommend the use of UV spectrophotometric analysis at 205-210 nm and 280 nm for estimating protein concentrations, respectively (Baily, JL., Techniques in Protein Chemistry, 2nd Ed., pp. 342-346, Elsevier Publishing Co., 1967).

We recommend the determination of lipase, amylase and protease to characterize the catalytic activity of the drug product per dosage unit. We would also like to point out that lipase potency is the absolute criteria for product activity and identity. Identification and characterization of pancrelipase containing products need to be based on catalytic activity; e.g. ability to hydrolyze lipid substrate (triglycerides) into free fatty acids and monoacyl glycerol, proteins into peptides and amino acids, and starches into dextrins and maltose as determined by official USP test methods.

Establishing lipase, amylase, and protease enzyme ratio specification for the finished drug product is impractical and unachievable.

Stability of Digestive Enzymes in Formulations:

- *Overly conservative tightening of specifications will unnecessarily reduce shelf life and increase costs without adding safety or efficacy benefits.*
- *Overages have been acceptable to the Agency.*
- *Overages of 140% are potentially acceptable for shelf life of two (2) years.*

The draft guidance provides that "primary stability data should be generated according to the guidance developed in ICH Q1A and Q5C". While there are many sound practices to be found in these ICH guidelines, there are also stability testing requirements that are impractical or impossible to apply to Pancreatic Enzyme Products (PEPs). For instance, identification of degradation products would be difficult and unnecessary. It would be difficult because the degradation products of PEPs constitute a complex and variable population of polypeptides, peptides, and amino acids. It would be unnecessary because of the manifest safety of these degradation products, which can be viewed as digestion products of an edible organ meat. ***We suggest that these concerns could be resolved by amendment of the draft guidance to provide that primary stability data should be generated utilizing validated methods and procedures including those provided by ICH Q1A and Q5C, where appropriate.***

The requirements of performing stability testing at 100% of the label claim potency, and not allowing for a range wide enough to support a reasonable overage and shelf life, will lead to an extremely short shelf life (less than one year) and this will have profound economic consequences throughout the chain of distribution. It could also adversely affect the clinical outcome of patients using these drugs. Shorter shelf life will result in more expired, returned, and wasted product. Manufacturing campaigns for different dosage strengths will have to be shorter or campaigning may have to be abandoned and parallel manufacturing lines established at increased capital and labor cost. Three major chain wholesalers account for approximately 90% of the distribution of pharmaceutical products to retailers and hospitals. Each of these wholesalers has strict requirements regarding the acceptance and handling of products based on the expiration dating. All three remove products from their shelves months ahead of expiration, which further shortens potential time in the distribution chain. Thus, distributors and pharmacies will have increased inventory management costs. The patient's risk of running out of supply will be increased because any disruption in production or transportation will cause an almost immediate shortage, since inventories will necessarily be kept low to minimize the costs of out-of-date returns. ***The overall economical impact of the short shelf life is that the cost of PEPs will approach the cost of other short shelf-life medications, such as vaccines.***

Testing at 100% of the label claim potency and having a proposed shelf life that does not depend on a stability overage will not result in physicians being able to more accurately

prescribe PEPs. The variability represented by the stability overage is overshadowed by the variability associated with varying fat content and amounts of meal and patient digestive differences. Physicians will still have to titrate patients to achieve optimal dosage. We also note that labeled potency of PEPs is only indicative of their biological potency in actual use. Lipase activity is pH dependent. The hydrolysis of triglycerides at pHs of 8.0, 7.0, and 6.0 proceed at approximately 70%, 24% and <1%, respectively, of the activity measured at the optimal pH of 9.0 Label potency of PEPs is determined at pH 9.0, whereas the pH in the small intestine is approximately 7.5-6.5 or lower, depending on meal and patient factors, which results in 49% to 97% less enzyme activity at the site of action than label claim.

It has also been our experience over the past 30(+) years that lipase activity degrades at a rate of about 8-12% per year in the pancrelipase drug substance due to several issues, some of which are difficult to control such as inherent protease activity and moisture. Present USP standards for PEPs have been set to 90-165%, presumably to account for these issues. ***Based on our extensive experience with these pancrelipase products, tightening the upper limit for overages to at least 140% would provide a two-year shelf life and satisfy a lower stability limit of 90% and still safely meet the needs of patients within the normal prescribing practice and use.***

This proposed range would be in line with some of the other classical biologicals as indicated in the examples above for chorionic gonadotropins and menotropins. Physicians have safely and effectively used these products with 45% variability (80-125%) despite the fact that ovarian hyper stimulation, in the case of menotropins, occurs much more frequently than fibrosing colonopathy in cystic fibrosis.

NON-CLINICAL PHARMACOLOGY AND TOXICOLOGY:

We concur with FDA's position that no new non-clinical studies are required for products which have been safely and effectively used in patients for some 50 years.

Human Pharmacokinetics and Bioavailability Section:

- *Pharmacokinetics intubation studies are very difficult to perform in the intestinal milieu of cystic fibrosis patients and are subject to large patient-to-patient variability.*
- *Intubation studies in children are technically more difficult than in adults.*
- *Safety and efficacy in clinical studies should be sufficient.*

The demonstration of bioavailability of the exogenously administered pancreatic enzymes in the intestine requires intubation with a multi-lumen gastrointestinal tube and the aspiration of the gastrointestinal contents for subsequent *in vitro* analysis of the enzymes for biological activity. The majority of the intubations have been carried out with adult patients in the fasting state and by employing a triple-lumen gastrointestinal tube under fluoroscopic guidance. One lumen is positioned in the stomach to aspirate out the gastric juice from the stomach while the second

and third lumens are positioned in the duodenum and the upper intestine 10-20 cm from the ligament of Treitz, respectively. The procedure to position the lumens usually takes 35-45 minutes under optimal conditions. Since the gastrointestinal tube is rubbed against the gastrointestinal mucosa with every swallowing of saliva, it causes stimulation of the gastrointestinal mucosa that, in turn, releases endogenous hormones to prompt the release of secretin and cholecystokinin (CCK) into the blood stream. The released secretin/CCK, in turn, activates the pancreas to release some preformed enzymes into the duodenum. Collections of the duodenal juices over a 30-60 minute period usually provide sufficient volume of pancreatic secretion to establish baseline collection levels. Infusion of a bolus dose of exogenously administered secretin/CCK is administered to deplete the pancreatic reserves from all pre-synthesized and stored enzymes. Collection over a 60-90 minute period yields maximum enzyme levels in the initial 15-45 minute stimulation period, followed by a precipitous drop of enzyme secretion and the establishment of pre-hormone stimulated conditions. At this point five (5) pancrelipase capsules are administered to the patient with a glass of water, followed by additional liquid or a test meal to simulate ingestion of a meal. The gastric lumen is clamped to prevent aspiration of the gastric content while the duodenal and the upper intestinal lumen are aspirated to collect the intestinal contents for *in vitro* analysis of the released active enzymes from the exogenously administered capsules for the next two hours. The results showed that some of the enzymes are released in the duodenum and greater amounts of the enzymes are released in the jejunum or further down the intestine. A total of four to five hours are required to achieve desirable collection conditions and obtain sufficient quantity of samples for the *in vitro* enzyme assays.

Recently a seven-lumen gastrointestinal tube was developed to reach even further down the intestine to obtain samples from the upper (duodenum), middle (jejunum) and lower (ileum) intestine. Three (3) adult cystic fibrosis patients were intubated with the seven-lumen gastrointestinal tube and marker perfusion technique (Butt AM, *et.al.*, 14th NASPGN Meeting, Orlando, Florida, 2001). Intestinal samples aspirated over seven and a half (7.5) hours were analyzed for enzyme activities, pH markers and bile acids. Studies with one of the commercially-marketed, enteric-coated formulation showed that the exogenously administered pancrelipase was mostly released in the jejunum (1-2.5 hours) and ileum.

The employment of the intubation procedure to demonstrate delivery of exogenous enzymes into the intestine in their biologically active state is complex, time-consuming and prohibitively expensive. Intubations are invasive, damages the lining of the esophagus, stimulate the gagging reflexes, are uncomfortable and painful. Furthermore, intubations in children are extremely difficult and, in most cases, parental permission is denied. Institutional Review Board (IRB) approval is also unlikely since the gained information contributes very little to our knowledge of intraluminal digestion of a meal and the resolution of steatorrhea. Therefore, intubation procedures are unjustified and not recommended for the *in situ* analysis of pancrelipase containing drug products. We urge the Agency to waive this requirement for measuring aspirates from the gastrointestinal tract and replace it with measurements of

acceptable pharmacodynamic endpoints. ***The primary end point of clinical effectiveness is the resolution of steatorrhea and that is a readily measured parameter.***

At the FDA-sponsored meeting of April 23, 1992 ("Exocrine Pancreatic Insufficiency Drug Product Workshop, FDA Memorandum of Meeting"), it was also stated "***in vitro*** measurement of enzyme activity complements the clinical efficacy determination, and ***in vivo*** measurement of enzyme activity is possible but is not a reliable indicator. The end point is not the enzyme activity that you will measure in the duodenal fluid. The end point is the steatorrhea that you are resolving" (Lebenthal, pg. 48).

CLINICAL STUDIES

We concur with many points in this section of the guideline as it relates to clinical trial considerations, patient population, endpoints, safety, and design. We shall only comment on those sections which we believe needs further consideration.

Considerations for Clinical Trial Development:

- *Dose-response relationship in clinical trials is not achievable with pancrelipase due to patient variability (patients are normally titrated by physicians).*

Establishing an empirical dose-response relationship in clinical trials, in our opinion, is not warranted with pancrelipase drug products due to large differences in between-subject variability and the fat content of meals on which the efficacy parameter is based. In addition, all patients, in conjunction with medical care, determine their optimal dose. Further, in order to establish such a relationship, a minimum of four dose levels are needed. The sample size required for such a trial would be extremely large. Given that the FDA has recognized that 10-25 patients are sufficient for pivotal trials, the necessity for conducting such a large dose-response trial is not necessary, onerous, impractical, and probably not achievable.

There are numerous example of drugs, both in the classical biologics category; *e.g.* menotropins, as well as chemically synthesized drugs; *e.g.* antidepressants approved by the FDA that do not or have not been able to demonstrate dose-response relationships.

Design:

- *A 72-hour stool analysis is one established and valid quantitative measure of steatorrhea.*
- *Baseline can be more suitably established by stool markers.*

It is appropriate that the FDA has considered several designs to establish efficacy, as well as the use of other active PEPs as comparators. A 72-hour stool analysis is an established and valid quantitative measure and remains a standard for the primary efficacy endpoint, the

resolution of steatorrhea. The concept that baseline conditions should be re-established in this indication does not make clinical sense. The effects on GI symptoms and fat malabsorption are instantaneous, localized, and short lived. Patients need to take their medication with each meal and this drug class has a short half life in the GI tract, their site of action, due to normal protease activity that hydrolyzes all proteins to peptides and amino acids. To account for any carryover effects, studies should be designed so that fecal fat is measured over the course of three days and should be done at the end of at least seven days of treatment. Stool markers can then be used to confirm that the stool measurements are taken at the correct time points and intervals.

End Points (Outcome Measures) Efficacy:

Clinical benefit can only be demonstrated under carefully defined conditions, such as control of defined diet with adequate intake of fat/protein/carbohydrates, use of stool markers for the 72-hour stool collection under supervised condition and preferably in the metabolic ward (Brady SM, et.al., Twelfth Annual North American CF Conference, 1998). The use of placebo as a reference control is unethical and unwarranted. We recommend the use of the commercially available enteric-coated pancrelipase product as reference controls. The positive control should be from a single lot, and before use, the lipase potency should be determined. Likewise, the test product's lipase potency should also be determined and matched up to the positive control lipase potency. This would ensure a dose-to-dose comparison of the test product to the reference positive control drug. We agree that the study population should include not more than 10 to 25 pancreatic enzyme insufficient cystic fibrosis patients. Fecal elastase assay should be evaluated as a potential pre-screening tool to confirm pancreatic enzyme insufficiency.

Once any product is demonstrated to be effective by the fecal fat analysis to resolve steatorrhea, additional product line extensions, *e.g.* change in dosage unit, two capsules reduced to one dosage unit, different capsule sizes, change in packaging, *etc.*, demonstration of effectiveness could be done with use of appropriate PD endpoints. These PD endpoints include common digestive signs and symptoms of stool frequency, stool consistency, urgency of bowel movements, intestinal gas and cramps, *etc.* This should be sufficient to demonstrate clinical effectiveness of the line extension of clinically proven products.

PEDIATRIC STUDIES FOR PEPs

Since pediatric patients form a large part of the target population, it is essential to include this age group in PEP studies. Rather than using separate studies, however, we would like the Agency to allow the use of pediatric subgroup analysis for clinical trials. Perhaps this was understood as a general procedure for clinical trials; nevertheless, we would like to encourage the FDA to include this in their guideline.

We hope that the Agency seriously considers our proposed recommendation in a positive light as improvement to the regulation of PEP products and not as overt criticism.

SUMMARY

In conclusion, DCI comments and recommendations are as follows.

Chemistry, Manufacturing, and Controls Section of the Application:

- We recommend the determination of lipase, amylase, and protease to characterize the catalytic activity of the drug product per dosage unit. Lipase potency is the absolute criteria for product activity and identity. Identification and characterization of pancrelipase containing product needs to be based on catalytic activity; *e.g.* able to hydrolyze lipid substrate (triglycerides) into free fatty acids and monoacyl glycerol, proteins into peptides and amino acids, and starches into dextrins and maltose as determined by official USP test methods.

- Establishing lipase, amylase, and protease enzyme ratio specification for the finished drug product is impractical and unachievable.

- Isoelectric focusing, SDS-PAGE electrophoresis or HPLC techniques are not suitable for the identification and characterization of pancrelipase extracts.

- The IR spectrophotometric method, employing the KBr pellet technique, is useful for the physico-chemical identification and characterization of pancrelipase drug substance and drug product.

- Excessive tightening of specifications will result in a short shelf life that will significantly increase costs without adding safety benefits. The overall economic impact of a short shelf life is that the cost of PEPs will approach the cost of other short shelf-life medications, such as vaccines.

- Based on our extensive experience of 30(+) years with these pancrelipase products, allowing for overages of at least 140% would provide a two-year shelf life and satisfy a lower stability limit of 90% and still safely meet the needs of patients within the normal prescribing practice and use.

Human Pharmacokinetics and Bioavailability Section:

- Intubation procedures to demonstrate delivery of exogenous enzymes into the intestine in their biologically active state is unjustified and unnecessary in the light of readily available PD markers of efficacy. These procedures are complex, time consuming, invasive, uncomfortable, painful, and prohibitively expensive. They can damage the

lining of the esophagus and stimulate the gagging reflex and, thus, compromise interpretations of data.

- We urge the Agency to waive this requirement.

Clinical Studies for New PEPs:

- Dose-response relationship in clinical trials is probably unachievable, impractical, and should not be required since the patients are normally titrated by physicians.

- A 72-hour stool analysis is one established and valid quantitative measure of steatorrhea. Stool markers can more suitably establish baseline.

- Efficacy of product line extensions should be based on clinical signs and symptoms.

Pediatric Studies for PEPs:

- We would like to encourage the FDA to include pediatric subgroup analysis for clinical trials in their guidelines.

Miscellaneous Items:

We would like to advocate the assembly of an expert panel to discuss many of the issues and concerns expressed by manufacturers and end users of pancreatic enzyme products in a public forum.

If you have any questions concerning these recommendations, please contact me by telephone at (610) 882-5950 or by e-mail at tibsipos@fast.net. Digestive Care, Inc. is pleased to send representatives of the company to the FDA to discuss concerns and recommendations with the Agency, if the need should arise, in the Fall of 2004. Your cooperation concerning this matter is greatly appreciated.

Sincerely,

TIBOR SIPOS, Ph.D.
President